REMARKS/ARGUMENTS

The foregoing amendments in the specification and claims are of a formal nature, and do not add new matter.

Prior to the present amendment, Claims 28-40 were pending in this application and were rejected on various grounds. With this amendment, Claims 36-37 have been canceled without prejudice and Claims 28-35 have been amended to clarify what Applicants have always regarded as their invention. The amendments to the specification and claims are fully supported by the specification and claims as originally filed and do not constitute new matter. Support for the amendments to Claims 28-32 can be found in Example 143 at least starting on page 494, line 20 of the specification.

Claims 28-35 and 38-40 are pending after entry of the instant amendment. Applicants expressly reserve the right to pursue any canceled matter in subsequent continuation, divisional or continuation-in-part applications.

In addition, Applicants request the PTO to take note of the Revocation and Power of Attorney and Change of Address filed on February 28, 2003 and kindly direct all future correspondence to the address indicated, *i.e.*, to:

CUSTOMER NO. 35489
Ginger R. Dreger
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Information Disclosure Statement

Applicants respectfully thank the Examiner for considering the Information Disclosure Statements filed on September 11, 2002 and November 5, 2002.

Specification

As requested by the Examiner, the specification has been amended to remove embedded hyperlink and/or other form of browser-executable code, and the title of the application has been

amended to recite a new, descriptive title indicative of the invention to which the claims are directed.

Further, Applicants have amended the specification to clearly recite the conditions of the deposits made under the Budapest Treaty.

Claim Rejections – 35 U.S.C. §101

Claims 28-40 stand rejected under 35 U.S.C. §101 allegedly "because the claimed invention is not supported by a specific, substantial and credible asserted utility or a well-established utility." (Page 3 of the instant Office Action). The Examiner alleges that "the specification does not teach any significance or functional characteristics of the PRO1759 polynucleotide (SEQ ID NO:373) or polypeptide (SEQ ID NO:374). The specification also does not disclose any methods or working examples that indicate the polynucleotides and polypeptide of the instant invention are involved in any activity."

Applicants respectfully disagree and traverse the rejection.

Applicants submit that the cancellation of Claims 36 and 37 and renders the rejection of these claims moot. Applicants further submit, for the reasons set forth below, that the specification discloses at least one credible, substantial and specific asserted utility for the polypeptide PRO1759.

Utility – Legal Standard

According to the Utility Examination Guidelines ("Utility Guidelines"), 66 Fed. Reg. 1092 (2001) an invention complies with the utility requirement of 35 U.S.C. §101, if it has at least one asserted "specific, substantial, and credible utility" or a "well-established utility."

Under the Utility Guidelines, a utility is "specific" when it is particular to the subject matter claimed. For example, it is generally not enough to state that a nucleic acid is useful as a diagnostic without also identifying the conditions that is to be diagnosed.

The requirement of "substantial utility" defines a "real world" use, and derives from the Supreme Court's holding in *Brenner v. Manson*, 383 U.S. 519, 534 (1966) stating that "[t]he basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility." In

explaining the "substantial utility" standard, M.P.E.P. §2107.01 cautions, however, that Office personnel must be careful not to interpret the phrase "immediate benefit to the public" or similar formulations used in certain court decisions to mean that products or services based on the claimed invention must be "currently available" to the public in order to satisfy the utility requirement. "Rather, **any reasonable use that an applicant has identified for the invention that can be viewed as providing a public benefit should be accepted as sufficient**, at least with regard to defining a "'substantial'" utility.'" (M.P.E.P. §2107.01, emphasis added.) Indeed, the Guidelines for Examination of Applications for Compliance With the Utility Requirement, set forth in M.P.E.P. §2107 II (B) (1) gives the following instruction to patent examiners: "If the applicant has asserted that the claimed invention is useful for any particular practical purpose . . . and the assertion would be considered credible by a person of ordinary skill in the art, do not impose a rejection based on lack of utility."

Finally, the Utility Guidelines restate the Patent Office's long established position that any asserted utility has to be "credible." "Credibility is assessed from the perspective of one of ordinary skill in the art in view of the disclosure and any other evidence of record . . . that is probative of the applicant's assertions." (M.P.E.P. §2107 II (B) (1) (ii)) Such a standard is presumptively satisfied unless the logic underlying the assertion is seriously flawed, or if the facts upon which the assertion is based are inconsistent with the logic underlying the assertion (Revised Interim Utility Guidelines Training Materials, 1999).

Utility – Application of Standard

Applicants rely on the gene amplification data to establish patentable utility for the PRO1759 polypeptide. Further, the Examiner has admitted that the nucleic acid encoding the PRO1759 polypeptide is amplified in three lung and colon tumors (HF-000840, HF-000795 and HF-001296). (See page 6 of the instant Office Action).

The Examiner asserts that the Examiner "is unable to find, either in the specification or in the art, an explanation of how ΔCt values are calculated, nor what the significance of such are."

In response, Applicants submit that it is well known in the art at the time the invention was made that gene amplification is an essential mechanism for oncogene activation. The gene

amplification assay is well-described in Example 143 of the present application, the inventors isolated genomic DNA from a variety of primary cancers and cancer cell lines that are listed in Table 8, including primary lung and colon tumors of the type and stage indicated in Table 7. As a negative control, DNA was isolated from the cells of ten normal healthy individuals, which was pooled and used as a control. Gene amplification was monitored using real-time quantitative TaqMan PCR. Table 7 shows the resulting gene amplification data. Further, Example 143 explains that the results of TaqMan™ PCR are reported in ΔCt units, wherein one unit corresponds to one PCR cycle or approximately a 2-fold amplification relative to control, two units correspond to 4-fold amplification, 3 units to 8-fold amplification etc.

Applicants respectfully submit that the specification discloses that the nucleic acids encoding PRO1759 had ΔCt value of > 1.0, which is **more than 2-fold increase**, in at least 3 of the tumors listed in Table 8.

Because amplification of the nucleic acid encoding PRO1759 occurs in lung and colon tumors, it is likely associated with lung and colon tumor formation and/or growth. As a result, antagonists (*e.g.*, antibodies) directed against PRO1759 would be expected to be useful in cancer therapy.

It is also well known that gene amplification occurs in most solid tumors, and generally is associated with poor prognosis.

In support, Applicants submit a Declaration by Dr. Audrey Goddard with this response and particularly draw the Examiner's attention to page 3 of the declaration which clearly states that:

> It is further my considered scientific opinion that an at least **2-fold increase** in gene copy number in a tumor tissue sample relative to a normal (*i.e.*, non-tumor) sample is significant and useful in that the detected increase in gene copy number in the tumor sample relative to the normal sample serves as a basis for using relative gene copy number as quantitated by the TaqMan PCR technique as a diagnostic marker for the presence or absence of tumor in a tissue sample of unknown pathology. Accordingly, a gene identified as being amplified at least 2-fold by the quantitative TaqMan PCR assay in a tumor sample relative to a normal sample is **useful as a marker for the diagnosis of cancer**, for monitoring cancer development and/or for measuring the efficacy of cancer therapy. (Emphasis added).

The attached Declaration by Audrey Goddard clearly establishes that the TaqMan real-time PCR method described in Example 143 has gained wide recognition for its versatility, sensitivity and accuracy, and is in extensive use for the study of gene amplification. The facts disclosed in the Declaration also confirm that based upon the gene amplification results, one of ordinary skill would find it credible that PRO1759 is a useful target for therapeutic intervention in lung and colon tumors.

Secondly, Applicants submit, as discussed below, that the Examiner has not established a *prima facie* case for lack of utility for PRO1759 polypeptide.

A prima facie case of lack of utility has not been established

The Examiner bases the conclusion of lack of utility on a quote from Pennica *et al.* According to the quoted statement, "WISP-1 gene amplification in human colon tumors showed a correlation between DNA amplification and over-expression, whereas overexpression of WISP-3 RNA was seen in the absence of DNA amplification. In contrast, WISP-2 DNA was amplified in colon tumors, but its mRNA expression was significantly reduced in the majority of tumors compared with expression in normal colonic mucosa from the same patient." From this, the Examiner correctly concludes that increased copy number does not *necessarily* result in increased polypeptide expression. The standard, however, is not absolute certainty. The fact that in the case of a specific class of closely related molecules there seemed to be no correlation with gene amplification and the level of mRNA/protein expression, does not establish that it is more likely than not, in general, that such correlation does not exist. The Examiner has not shown whether the lack or correlation observed for the family of WISP polypeptides is typical, or is merely a discrepancy, an exception to the rule of correlation. Indeed, the working hypothesis among those skilled in the art is that, if a gene is amplified in cancer, the encoded protein is likely to be expressed at an elevated level. In fact, as noted even in Pennica *et al.*, a correlation between DNA amplification and over-expression of polypeptide **was observed** in the case of WISP-1.

The Examiner also cites the Haynes *et al.* reference to establish that "protein expression levels cannot be accurately predicted from the level of corresponding mRNA transcript." The Examiner adds that "Haynes *et al.* studied 80 proteins ... and found no strong correlation

between proteins and transcript levels." Applicants respectfully traverse and point out that, on the contrary, Haynes teaches that "*there was a general trend* but no strong correlation between protein [expression] and transcript levels" (See page 1863, under Section 2.1, emphasis added). Haynes studied 80 *yeast* proteins to show that "protein levels cannot be *accurately* predicted from the level of the corresponding mRNA transcript" (See page 1863, under Section 2.1, last line, emphasis added). For example, in Figure 1, there is a positive correlation between mRNA and protein amongst *most* of the 80 yeast proteins studied but the correlation is not linear, hence authors suggest that one cannot *accurately* predict protein levels from mRNA levels. In fact, very few data points deviated or scattered away from the expected normal or showed a lack of correlation between mRNA: protein levels. Thus, the Haynes data meets the "more likely than not standard" and shows that a positive correlation exists between mRNA and protein. Therefore, Applicants respectfully submit that the Examiner's rejection is based on a misrepresentation of the data presented in Haynes *et al.*

Accordingly, as stated above, since the standard is not absolute certainty, a *prima facie* showing of lack of utility has not been made in this instance and the burden to provide further evidence of utility has not shifted to Applicants.

Further, the Examiner asserts that "[t]he data presented in the specification were not corrected for aneuploidy." Thus, the Examiner concludes, "A slight amplification of a gene does not *necessarily* mean overexpression in a cancer tissue, but can merely be an indication that the cancer tissue is aneuploid."

In response, Applicants respectfully submit a Declaration by Dr. Avi Ashkenazi, Ph.D., an expert in the field of cancer biology and an inventor of the present application. As Dr. Ashkenazi explains,

> An increase in gene copy number can result not only from intrachromosomal changes but also from chromosomal aneuploidy. It is important to understand that detection of gene amplification can be used for cancer diagnosis even if the determination includes measurement of chromosomal aneuploidy. Indeed, as long as a significant difference relative to normal tissue is detected, it is irrelevant if the signal originates from an increase in the number of gene copies per chromosome and/or an abnormal number of chromosomes.

Hence, Applicants respectfully submit that gene amplification of a gene, whether by aneuploidy or any other mechanism, is still useful as a diagnostic marker.

Even if a prima facie case of lack of utility had been established, it should be withdrawn on consideration of the totality of evidence

Even if one assumes arguendo that it is more likely than not that there is no correlation between gene amplification and increased mRNA/protein expression, a polypeptide encoded by a gene that is amplified in cancer would still have a specific and substantial utility. In support, Applicants draw the Examiner's attention to page 2 of Dr. Avi Ashkenazi's Declaration which explains that,

> even when amplification of a cancer marker gene does not result in significant over-expression of the corresponding gene product, this very absence of gene product over-expression still provides significant information for cancer diagnosis and treatment. Thus, if over-expression of the gene product does not parallel gene amplification in certain tumor types but does so in others, then parallel monitoring of gene amplification and gene product over-expression enables more accurate tumor classification and hence better determination of suitable therapy. In addition, absence of over-expression is crucial information for the practicing clinician. If a gene is amplified but the corresponding gene product is not over-expressed, the clinician accordingly will decide not to treat a patient with agents that target that gene product.

Applicants thus submit that simultaneous testing of gene amplification and gene product over-expression enables more accurate tumor classification, even if the gene-product, the protein, is not over-expressed. This leads to better determination of a suitable therapy. Further, as explained in Dr. Ashkenazi's Declaration, absence of over-expression of the protein itself is crucial information for the practicing clinician. If a gene is amplified in a tumor, but the corresponding gene product is not over-expressed, the clinician will decide not to treat a patient with agents that target that gene product. This not only saves money, but also the patient need not be exposed to the side effects associated with such agents.

This is further supported by the teachings of the attached article by Hanna and Mornin. (Pathology Associates Medical Laboratories, August (1999), copy enclosed). The article teaches that the HER-2/neu gene has been shown to be amplified and/or over-expressed in 10%-30% of

invasive breast cancers and in 40%-60% of intraductal breast carcinoma. Further, the article teaches that diagnosis of breast cancer includes testing both the amplification of the HER-2/neu gene (by FISH) as well as the over-expression of the HER-2/neu gene product (by IHC). Even when the protein is not over-expressed, the assay relying on both tests leads to a more accurate classification of the cancer and a more effective treatment of it.

Applicants also submit that there are numerous articles which show that generally, if a gene is amplified in cancer, it is more likely than not that the encoded protein will be expressed at an elevated level. For example, Orntoft *et al.* (*Mol. and Cell. Proteomics*, 2002, Vol.1, pages 37-45, copy enclosed) studied transcript levels of 5600 genes in malignant bladder cancers many of which were linked to the gain or loss of chromosomal material using an array-based method. Orntoft *et al.* showed that there was a gene dosage effect and taught that "in general (18 of 23 cases) chromosomal areas with more than 2-fold gain of DNA showed a corresponding increase in mRNA transcripts" (see column 1, abstract). In addition, Hyman *et al.* (*Cancer Res.*, 2002, Vol. 62, pages 6240-45, copy enclosed) showed, using CGH analysis and cDNA microarrays which compared DNA copy numbers and mRNA expression of over 12,000 genes in breast cancer tumors and cell lines, that there was "evidence of a prominent global influence of copy number changes on gene expression levels." (See page 6244, column 1, last paragraph). Additional supportive teachings were also provided by Pollack *et al.*, (*PNAS*, 2002, Vol. 99, pages 12963-12968, copy enclosed) who studied a series of primary human breast tumors and showed that "62% of highly amplified genes show moderately or highly elevated expression, and DNA copy number influences gene expression across a wide range of DNA copy number alterations (deletion, low-, mid- and high-level amplification), and that on average, a 2-fold change in DNA copy number is associated with a corresponding 1.5-fold change in mRNA levels." Thus, these articles collectively teach that in general, gene amplification increases mRNA expression.

Finally, enclosed is a Declaration by Dr. Polakis, principal investigator of the Tumor Antigen Project of Genentech, Inc., the assignee of the present application, to show that mRNA expression correlates well with protein levels, in general. As Dr. Polakis explains, the primary focus of the microarray project was to identify tumor cell markers useful as targets for both the

diagnosis and treatment of cancer in humans. The scientists working on the project extensively rely on results of microarray experiments in their effort to identify such markers. As Dr. Polakis explains, using microarray analysis, Genentech scientists have identified approximately 200 gene transcripts (mRNAs) that are present in human tumor cells at significantly higher levels than in corresponding normal human cells. To date, they have generated antibodies that bind to about 30 of the tumor antigen proteins expressed from these differentially expressed gene transcripts and have used these antibodies to quantitatively determine the level of production of these tumor antigen proteins in both human cancer cells and corresponding normal cells. Having compared the levels of mRNA and protein in both the tumor and normal cells analyzed, they found a very good correlation between mRNA and corresponding protein levels. Specifically, in approximately 80% of their observations they have found that increases in the level of a particular mRNA correlates with changes in the level of protein expressed from that mRNA. While the proper legal standard is to show that the existence of correlation between mRNA and polypeptide levels is more likely than not, the showing of approximately 80% correlation for the molecules tested in the Polakis Declaration greatly exceed this legal standard. Based on these experimental data and his vast scientific experience of more than 20 years, Dr. Polakis states that, for human genes, increased mRNA levels typically correlate with an increase in abundance of the encoded protein. He further confirms that "it remains a central dogma in molecular biology that increased mRNA levels are predictive of corresponding increased levels of the encoded protein."

Taken together, although there are some examples in the scientific art that do not fit within the central dogma of molecular biology that there is a correlation between polypeptide and mRNA levels, these instances are exceptions rather than the rule. In the majority of amplified genes, the teachings in the art, as exemplified by Orntoft *et al.*, Hyman *et al.*, Pollack *et al.*, and the Polakis Declaration, overwhelmingly show that gene amplification influences gene expression at the mRNA and protein levels. Thus, one of skill in the art would reasonably expect in this instance, based on the amplification data for the PRO1759 gene, that the PRO1759 polypeptide is concomitantly over-expressed. Hence the PRO1759 polypeptides has utility in the diagnosis of cancer.

In view of the above, Applicants respectfully submit that the specification discloses at

least one credible, substantial and specific asserted utility for the PRO1759 polypeptide. Accordingly, the Examiner is requested to reconsider and withdraw the present rejection under 35 U.S.C. §101.

Claim Rejection - 35 U.S.C. §112, First Paragraph (Enablement)

Claims 28-40 stand rejected under 35 U.S.C. §112, first paragraph, allegedly since "the claimed invention is not supported by either a specific and substantial utility or a well established utility." In particular the Examiner asserts that "the specification does not teach any variant, fragment, or derivative of PRO1759 polypeptide other than the full-length amino acid sequence of SEQ ID NO:374. The specification also does not teach functional or structural characteristics of the polypeptide variants, fragments, and derivatives recited in the claims." (See instant Office Action, page 9).

Applicants respectfully disagree and traverse the rejection.

Applicants submit that the cancellation of Claims 36 and 37 renders the rejection of these claims moot.

Without acquiescing to the Examiner's position in the current rejections, and without prejudice to further prosecution of the subject-matter in one or more continuation or divisional applications, Claims 28-32 (and, as a consequence, those claims dependent from the same) are amended to recite a functional limitation that "the nucleic acid encoding the polypeptide is amplified in lung or colon tumors." Since the claimed genus is now characterized by a combination of structural and functional features, any person of skill would know how to make and use the invention without undue experimentation based on the general knowledge in the art at the time the invention was made. As the M.P.E.P. states, "The fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation" *In re Certain Limited-charge cell Culture Microcarriers, 221 USPQ 1165, 1174* (Int'l Trade Comm'n 1983), *aff'. sub nom., Massachusetts Institute of Technology v A.B. Fortia,* 774 F.2d 1104, 227 USPQ 428 (Fed. Cir. 1985) M.P.E.P. 2164.01. Accordingly, the Examiner is respectfully requested to reconsider and withdraw the present rejection.

Claim Rejection - 35 U.S.C. §112, First Paragraph (Written Description)

Claims 28-33, 36-37 and 39-40 are rejected under 35 USC 112, first paragraph, for allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors had possession of the claimed invention at the time the application was filed. In particular, the Examiner notes that "[t]he claims are directed to an isolated polypeptide having at least 80%, 85%, 90%, 95% or 99% sequence identity to ... SEQ ID NO:374 ... [without requiring] that the polypeptide possess any particular biological activity, nor any particular conserved structure, or other disclosed distinguishing feature. Thus, the claims are drawn to a genus of polypeptides that is defined only by sequence identity."

Applicants respectfully disagree and traverse the rejection.

Applicants submit that the cancellation of Claims 36 and 37 renders the rejection of these claims moot.

With regard to Claim 33, the Examiner has admitted that "an isolated polypeptide consisting of amino acid sequence of SEQ ID NO:374 ... meets the written description provision of 35 U.S.C. §112, first paragraph." (See page 11 of the instant Office Action).

Without acquiescing to the Examiner's position, and solely in the interest of expediting prosecution in this case, Claims 28-32 (and, as a consequence, those claims dependent from the same) are amended to recite a functional limitation that "the nucleic acid encoding the polypeptide is amplified in lung or colon tumors." Accordingly, it is no longer true that the claims are drawn to a genus of polynucleotides defined by sequence identity alone. This biological activity, coupled with a well defined, and relatively high degree of sequence identity are believed to sufficiently define the claimed genus, such that one skilled in the art would readily recognize that the Applicants were in the possession of the invention claimed at the effective filing date of this application. The Examiner is therefore respectfully requested to reconsider and withdraw the present rejection.

Claim Rejection - 35 U.S.C. §112, Second Paragraph

Claims 28-33, 36-37 and 39-40 are rejected under 35 U.S.C. §112, second paragraph, as

being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In particular, the Examiner alleges that the limitation that the claimed protein comprises an "extracellular domain" and the recitation of "lacking its associated signal peptide" are indefinite.

Applicants submit that the cancellation of Claims 36 and 37 and renders the rejection of these claims moot.

Without acquiescing to the Examiner's position, and solely in the interest of expediting prosecution in this case, as amended, the terms "extracellular domain" and "extracellular domain ... lacking its associated signal peptide" are no longer present in Claims 28-33 (and, as a consequence, those claims dependent from the same). Hence, the rejection is believed to be moot, and should be withdrawn.

CONCLUSION

All claims pending in the present application are believed to be in *prima facie* condition for allowance, and an early action to that effect is respectfully solicited.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. **08-1641**, referencing Attorney's Docket No. **39780-2830 P1C38**). Please direct any calls in connection with this application to the undersigned at the number provided below.

Respectfully submitted,

Date: February 2, 2005

By: _____
Anna L. Barry (Reg. No. 51,436)

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